Epidemiology and Prevention of Carbapenem-Resistant Enterobacteriaceae

Beacon Patient Safety Exchange
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Healthcare Associated Infections Program
California Department of Public Health
Objectives

• Describe the epidemiology of carbapenem-resistant *Enterobacteriaceae* (CRE) in the United States
• Review measures necessary to halt transmission
• Recognize the importance of a regional approach to CRE control
• Describe California CRE Prevalence Survey
**Enterobacteriaceae**

- Normal human gut flora & environmental organisms
- More than 70 species
- Range of human infections:
  - UTI, wound infections, pneumonia, bacteremia
- Important cause of healthcare and community-associated infections
  - Some of the most common organisms encountered in clinical laboratories
### Pathogens Reported to NHSN 2009-2010

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Overall percentage</th>
<th>CLABSI</th>
<th>CAUTI</th>
<th>VAP</th>
<th>SSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>12% (2)</td>
<td></td>
<td>4%</td>
<td></td>
<td>27%</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>8% (4)</td>
<td></td>
<td>8%</td>
<td></td>
<td>11%</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>8% (5)</td>
<td>4%</td>
<td>11%</td>
<td>17%</td>
<td>6%</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>5% (8)</td>
<td>5%</td>
<td>4%</td>
<td>9%</td>
<td>4%</td>
</tr>
</tbody>
</table>

These three groups of organisms make up ~25% of organisms reported to NHSN Device and Procedure module.

Treatment of Gram-Negative Pathogens

• β-lactam antibiotics (penicillin derivatives – including methicillin) first-line treatment
  – Emergence of resistance to β-lactam antibiotics began even before penicillin was developed
  – First β-lactamase identified in *E. coli*
  – Many Gram-negative pathogens possess naturally occurring, chromosomally mediated β-lactamase or have acquired plasmids, integrons conferring resistance
Specific Mechanisms of Resistance in Enterobacteriaceae

• Extended-spectrum β-lactamase (ESBLs)
  – Mediate resistance to 3rd generation cephalosporins, monobactams but not cephemycins or carbapenems
  – Usually nosocomial however 34% from patients with no healthcare contact
  – Multinational survey in nonhospitalized patients

• Risk Factors:
  – Male
  – >65 y/o
  – Recent antibiotic use
  – Resident of long-term care facility
  – Recent hospitalization

Fortunately, our most potent class of $\beta$-lactams, carbapenems, remained effective against almost all *Enterobacteriaceae*: Meropenem, Doripenem, Ertapenem, Imipenem

- Isolate collected in 1996 during an ICU surveillance project from NC
- Class A $\beta$-lactamase
**Klebsiella pneumoniae** carbapenememases (KPCs)

- A type of carbapenem-resistant *Enterobacteriaceae* (CRE)
  - Confers resistance to all β-lactams
  - Resides on transferable plasmids and hydrolyzes all penicillins, cephalosporins and carbapenems
  - Limits options for treatment
    - Polymyxins (problems with nephrotoxicity)
KPC

• No clinical data to indicate isolates with elevated but “sensitive” MICs fail therapy
• Spp.
  – Common – *Klebsiella pneumoniae*

Definitions of CRE

- Any *Enterobacteriaceae* spp. that are intermediate or resistant to at least one carbapenem and resistant to all third-generation cephalosporins tested (ceftriaxone, cefotaxime, and ceftazidime)

Or

- Any *Enterobacteriaceae* spp. that test positive for carbapenemase production by any method (e.g. Modified Hodge Test, disk diffusion, PCR)
Carbapenemase-producing CRE in the United States

CDC, unpublished data

Nov 2006
KPC-producing CRE in the United States

CDC, unpublished data

Courtesy of Alex Kallen, CDC
# Carbapenemases

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Classification</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPC</td>
<td>Class A</td>
<td>Hydrolyzes all β-lactam agents</td>
</tr>
<tr>
<td>NDM-1</td>
<td>Class B: metallo-β-lactamse (MBL)</td>
<td>Hydrolyzes all β-lactam agents except aztreonam</td>
</tr>
<tr>
<td>IMP</td>
<td>Class B: metallo-β-lactamse (MBL)</td>
<td>Hydrolyzes all β-lactam agents except aztreonam</td>
</tr>
<tr>
<td>VIM</td>
<td>Class D</td>
<td>Hydrolyzes carbapenems but not active against 3rd generation cephalosporins</td>
</tr>
<tr>
<td>OXA</td>
<td>Class D</td>
<td>Hydrolyzes carbapenems but not active against 3rd generation cephalosporins</td>
</tr>
</tbody>
</table>
Carbapenemase-producing CRE in the United States


CDC, unpublished data

Courtesy of Alex Kallen, CDC
<table>
<thead>
<tr>
<th>Organism</th>
<th>National Nosocomial infection Surveillance system, Number (%) of isolates</th>
<th>National Healthcare Safety Network, Number (%) of isolates</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Isolates</td>
<td>Tested</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae and oxytoca</strong></td>
<td>654</td>
<td>253</td>
</tr>
<tr>
<td></td>
<td>4 (1.6)</td>
<td></td>
</tr>
<tr>
<td><strong>E. coli</strong></td>
<td>1,424</td>
<td>421</td>
</tr>
<tr>
<td></td>
<td>4 (1.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Enterobacter aerogenes and cloacae</strong></td>
<td>553</td>
<td>288</td>
</tr>
<tr>
<td></td>
<td>4 (1.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2,631</td>
<td>962</td>
</tr>
<tr>
<td></td>
<td>12 (1.2)</td>
<td></td>
</tr>
</tbody>
</table>

Change in CRE incidence, 2001-2011

Courtesy of Alex Kallen, CDC
## Change in CRE incidence, 2001-2011

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<tbody>
<tr>
<td></td>
<td>Isolates</td>
<td>Tested</td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella pneumoniae and oxytoca</td>
<td>654</td>
<td>253 (38.7)</td>
</tr>
<tr>
<td>E. coli</td>
<td>1,424</td>
<td>421 (29.6)</td>
</tr>
<tr>
<td>Enterobacter aerogenes and cloacae</td>
<td>553</td>
<td>288 (52.1)</td>
</tr>
<tr>
<td>Total</td>
<td>2,631</td>
<td>962 (36.6)</td>
</tr>
</tbody>
</table>

*Courtesy of Alex Kallen, CDC*
Why are CRE Clinically and Epidemiologically Important?
Why are CRE Clinically and Epidemiologically Important?

• Cause infections associated with high mortality rates
Mortality

Overall Mortality
OR 3.71 (1.97-7.01)

Attributable Mortality
OR 4.5 (2.16-9.35)

Why are CRE Clinically and Epidemiologically Important?

• Cause infections associated with high mortality rates

• Resistance is highly transmissible
  • Between organisms – plasmids
  • Between patients
Why are CRE Clinically and Epidemiologically Important?

- Cause infections associated with high mortality rates
- Resistance is highly transmissible
- Treatment options are limited
  - Pan-resistant strains identified
  - Could be decades before new agents are available to treat
Why are CRE Clinically and Epidemiologically Important?

- Cause infections associated with high mortality rates
- Resistance is highly transmissible
- Treatment options are limited
- Potential for spread into the community
  - *E. coli* common cause of community infection
MDR GNRs in the Community

• NDM
  • Identified in *K. pneumoniae* in river in Hanoi, Viet Nam
  • Cause of community-onset infections in India
    • In one survey, isolates from 2 sites often from community acquired UTIs
  • Gene for NDM detected in 2/50 drinking water samples and 51/171 water seepage samples from New Delhi
  • One investigation of NDM identified family member of patient with NDM colonization

Isozumi R et al. EID 2012: 1383-4
Kumarasamy K Lancet ID 2010;
Walsh TR Lancet ID 2011:355-362
Why are CRE Clinically and Epidemiologically Important?

- Cause infections associated with high mortality rates
- Resistance is highly transmissible
- Treatment options are limited
- Potential for spread into the community
- In most areas in the United States this organism appears to be infrequently identified
Facilities Reporting at least One CRE (CAUTI or CLABSI) to NHSN, First Half of 2012

<table>
<thead>
<tr>
<th>Facility characteristic</th>
<th>Number of facilities with CRE from a CAUTI or CLABSI (2012)</th>
<th>Total facilities performing CAUTI or CLABSI surveillance (2012)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All acute care hospitals</td>
<td>181</td>
<td>3,918</td>
<td>(4.6)</td>
</tr>
<tr>
<td>Short-stay acute hospital</td>
<td>145</td>
<td>3,716</td>
<td>(3.9)</td>
</tr>
<tr>
<td>Long-term acute care hospital</td>
<td>36</td>
<td>202</td>
<td>(17.8)</td>
</tr>
</tbody>
</table>

Courtesy of Alex Kallen, CDC
ROLE OF LONG-TERM CARE
KPC outbreak in Chicago, 2008

- Of 40 KPC patients, only 4 definitively acquired KPC in acute care hospital
- Most (60%) linked to 1 LTACH

CRE Prevalence in LTCF: By Type

Prevalence of CRE Carriage at admission to 4 acute care hospitals

- SNF: 1.5%
- VSNF: 27.3%
- LTACH: 33.3%
- LTCF overall: 8.3%

0% from those admitted from the community

Prabaker K et al. ICHE 2012; 33:1193-1199
Prevention

http://www.cdc.gov/hai/organisms/cre/cre-toolkit/

http://www.cdph.ca.gov/programs/hai/Pages/Carbapenem-ResistantEnterobacteriaceae.aspx
Surveillance and Definitions

- Facilities/Regions should have an awareness of the prevalence of CRE in their Facility/Region
  - Could concentrate on *Klebsiella* and *E. coli*
  - Could concentrate on those NS to a carbapenem OR add R to a third-generation cephalosporin to the definition to increase specificity for KPC
    - Ceftriaxone, cefotaxime, ceftazidime
- No easy way right now to check for carbapenemases
Interventions

• Core
  • Hand hygiene
  • Contact Precautions*
  • HCP education
  • Minimizing device use
  • Patient and Staff cohorting
  • Laboratory notification*
  • Antimicrobial stewardship
  • CRE Screening*

• Supplemental
  • Active surveillance cultures
  • Chlorhexidine bathing

* Included in 2009 document
Contact Precautions (CP)

- Patients colonized or infected with CRE
- Systems in place to identify patients at readmission
- Education of HCP about use and rationale behind CP
- Adherence monitoring
- Consideration of pre-emptive CP in patients transferred from high-risk settings
CP in Long-Term Care

• For residents with CRE who are at higher risk for transmission
  • Dependent upon HCP for their activities of daily living
  • Ventilator-dependent
  • Incontinent of stool
  • Wounds with drainage that are difficult to control
• For other residents the requirement for CPs might be relaxed
• Standard Precautions should be maintained
Duration of KPC Carriage

• KPC Patients swabbed 5 to 6 times (at discharge, 2 weeks, 1, 2, 3 mos post-discharge)
• Overall resolution of carriage (2 consecutive negatives)
  • 62/125 (52%)
  • 39% of recently identified patient
  • 79% of remotely identified patients (> 4 mos prior)

Number of Screens to Determine CRE Clearance

- One negative (N=97) – 65 (67%) cleared
- Two negative (N=67) – 57 (85%) cleared
- Three negative (N=50) – 45 (90%) cleared

**TABLE 2.** Validity of different criteria for defining clearance of KPC KP carriage

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Study group</th>
<th>Total number of patients, n</th>
<th>Patients with negative tests, n</th>
<th>Patients with KPC KP^b clearance, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>REC</td>
<td>≥ 2 tests</td>
<td>≥ 1 negative test</td>
<td>29 (54)</td>
</tr>
<tr>
<td></td>
<td>REM</td>
<td>49</td>
<td>43</td>
<td>36 (84)</td>
</tr>
<tr>
<td>2</td>
<td>REC</td>
<td>≥ 3 tests</td>
<td>≥ 2 negative tests</td>
<td>25 (81)</td>
</tr>
<tr>
<td></td>
<td>REM</td>
<td>55</td>
<td>31</td>
<td>32 (89)</td>
</tr>
<tr>
<td>3</td>
<td>REC</td>
<td>≥ 4 tests</td>
<td>≥ 3 negative tests</td>
<td>16 (84)</td>
</tr>
<tr>
<td></td>
<td>REM</td>
<td>52</td>
<td>31</td>
<td>29 (94)</td>
</tr>
</tbody>
</table>

^aCriteria, number of consecutive negative tests (without subsequent positive test) necessary for defining clearance of KPC KP carriage.
^bKPC KP, KPC-producing Klebsiella pneumoniae.
^c%, ratio of the number of patients with KPC KP clearance to the number of patients with negative tests.
^dREC, recent (<4 months) KPC KP acquisition group.
^eREM, remote (>4 months) KPC KP acquisition group.
Patient and Staff Cohorting

- CRE patients in single rooms (when available)
- Cohorting (even when in single rooms)
- Staff cohorting
- Preference for single rooms should be given to patients at highest risk for transmission such as patients with incontinence, medical devices, or wounds with uncontrolled drainage
CRE Screening

• Studies suggest that only a minority of patients colonized with CRE will have positive clinical cultures
  
  • CRKP point prevalence study in Israel (5.4% prevalence rate); 5/16 had a positive clinical culture for CRKP
  
  • A study of surveillance cultures at a US hospital found that they identified a third of all positive CRKP patients. Not having these patients in CP resulted in about 1400 days of unprotected exposure.

Calfee et al. ICHE 2008;29:966-8
CRE Screening

- Used to identify unrecognized CRE colonization among contacts of CRE patients
- Stool, rectal, peri-rectal
- Link to CDC laboratory protocol:
  - [http://www.cdc.gov/ncidod/dhqp/pdf/ar/Klebsiella_or_E.coli.pdf](http://www.cdc.gov/ncidod/dhqp/pdf/ar/Klebsiella_or_E.coli.pdf)
- Applicable to both acute and long-term care settings
**CRE Screening: Types**

- Epidemiologically linked patients
  - Roommates
  - Patients who shared primary HCP
- Point prevalence survey
  - Rapid assessment of CRE prevalence on particular wards/units
  - Might be useful if lab review identifies one or more previously unrecognized CRE patient on a particular unit
Active Surveillance Cultures

• Screening patients (generally at admission) for CRE
• Controversial
• Potential considerations:
  • Focus on patients admitted to certain high-risk settings (e.g., ICU) or specific populations (e.g., from LTCF/LTAC)
  • Patients hospitalized outside the US
Chlorhexidine Bathing

- Limited evidence for CRE
  - Used effectively in outbreak in LTAC as part of a package of interventions
  - Applied to all patients regardless of CRE colonization status
  - Has shown decrease transmission of MRSA and VRE
- Some studies suggest CHG bathing may not be done “well”

Munoz-Price et al. ICHE 2010;31:341-7
REGIONAL APPROACH TO CRE PREVENTION
Inter-Facility Transmission of MDROs (Including CRE)

Figure 3. Patient flow among regional health care facilities. Outbreaks of infection with multidrug-resistant organisms have been found to follow the flow of colonized patients across institutions.
Israel Experience

• KPCs likely originally from US identified in Israel beginning in late 2005
• By early 2006, increase in cases
• Initiated national effort to control CRE
National Intervention to Control CRE: Israel

- Mandatory reporting
- Mandatory isolation of hospitalized CRE carriers
  - Contact precautions (index and subsequent admissions)
  - Cohort nursing
- National Task Force with authority to collect data and intervene as needed.

Schwaber MJ. *Clin Infect Dis* 2011;52(7):1-8
“An effective intervention at containing the spread of CRE should ideally be implemented before CRE have entered a region, or at the very least, immediately after its recognition. Policy makers and public health authorities must ensure the early recognition and coordinated control of CRE.”

Schwaber, MJ and Carmeli Y. *JAMA* December 2008;300:2911
Role of Public Health

- CDC has identified state health departments as key leaders in preventing the spread of CRE by assisting with:
  - Surveillance
  - Situational awareness
  - Coordinating prevention efforts
CDPH CRE Prevalence Survey

- Assess presence of carbapenem-resistant *Escherichia coli*, *Klebsiella pneumoniae* in each general acute care hospital in California
  - Educate infection control personnel on CRE
  - Utilize 2012 hospital-specific Antibiogram (susceptibility data)
  - Obtain contact information for laboratory director
  - Direct infection prevention personnel to CDC toolkit and CDPH website
CDPH CRE Prevalence Survey

• Classify general acute care hospitals into no, few or common CRE facilities
• Explore regional approach to CRE prevention
  • Educate hospitals on their regional prevalence of CRE
  • Facilitate healthcare facilities working within their regions to prevent or limit CRE
CDPH CRE Prevalence Survey

• Began May 2013 → ongoing
• IP will be contacted by CDPH staff
• Aim is to be completed by October 2013 for analysis
• Webinar to be held with hospitals January 2014
Summary

• Carbapenem-resistance among Enterobacteriaceae appears to be increasing
  • Driven primarily by the emergence of carbapenemases
• Heterogeneously distributed within and across regions
• Has the potential to spread widely
  • Healthcare and community settings
Summary

• Most areas in a position to act given slow emergence
  • Opportunity for prevention

• A regional approach to MDRO prevention is required
  • Public health well-positioned to facilitate and support regional prevention efforts
Questions?

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- (510)307-8940